SCIENTIFIC ABSTRACT

This gene transfer trial is the first epilepsy protocol to be submitted to the Recombinant DNA Advisory Committee. The principal investigators include Dr. During who has experience with both epilepsy research and gene transfer, and Drs. Fried and Stern who have extensive experience in both clinical epilepsy research and therapy including surgical trials. Moreover, the study is proposed to be conducted at UCLA, the institution which pioneered the use of long-term depth electrode recording in epilepsy, and is a major U.S. center for both epilepsy research and surgery. Mesial temporal lobe epilepsy subsequently referred to simply as TLE, is we believe an excellent indication for gene therapy, because although it is a complex acquired disease of unknown etiology, it is characterized by having a specific anatomical substrate, the mesial temporal lobe, specifically the hippocampus. Previous studies have shown that the epileptogenic hippocampus has altered physiology favoring excitation over inhibition. Simplistically this excitation/inhibition imbalance involves excessive glutamatergic excitation overpowering the inhibitory systems. Hence, strategies to treat epilepsy pharmacologically have largely addressed the inadequate inhibition or alternatively blocking the excitation at the level of transmitter receptors, metabolism or ion channels. Although these anti-epileptic drugs (AED) have some efficacy, approximately 30% of TLE patients remain refractory to two or more of the most active AED. This medically-intractable group of TLE may however benefit from surgery. Specifically, in carefully selected patients, success rates can run as high as 70% in the best centers, including UCLA. However, surgery comes at a cost, that is a major resection with all the attendant risks including deficits relating to any function that the resected brain region subserved. This is most commonly manifest as cognitive and memory loss, although pre-operative evaluation including the Wada test attempt to exclude subjects who are heavily dependent on the involved hemisphere for memory and verbal functions. Nevertheless, there is a significant complication rate, but this is offset by the marked benefit that typically follows surgical resection. The goal of the current protocol is to undertake an initial safety (Phase I) study which will provide safety and tolerance data to support a subsequent more definitive Phase II study to demonstrate that gene transfer using an adeno-associated virus expressing NPY is beneficial in TLE with less risk than those

associated with temporal lobectomy. We have chosen NPY as the transgene because of extensive and consistent data in both experimental animal models as well as supportive physiological and anatomical studies of human epileptic tissue. A critical component of the current study is that we propose to "piggy-back" on a clinically-indicated surgery, that is the implantation of depth electrodes for surgical evaluation. Hence, the gene transfer requires no additional invasive procedure, the intervention that provides the most potential risk. The second aspect of this protocol which lowers the risk threshold is that all patients who will be asked to volunteer for the study will already have agreed to undergo resective surgery of the very temporal lobe in which the viral vector is injected. The only variance from standard clinical care is that the surgical resection will be delayed, from what typically is scheduled for 2-4 months following intracranial recording, to 6 months. Thus the risks associated with this trial include those related to the use of AAV and the specific transgene NPY, but this is offset by no additional surgery to introduce the genetic material, plus the built-in "rescue" procedure, wherein the transduced cells are removed en bloc in a subsequent clinically-indicated and therapeutic procedure. We believe that this design provides an acceptable risk/benefit ratio with strong preclinical data on potential efficacy, and previous clinical experience suggesting minimal likelihood of adverse events.